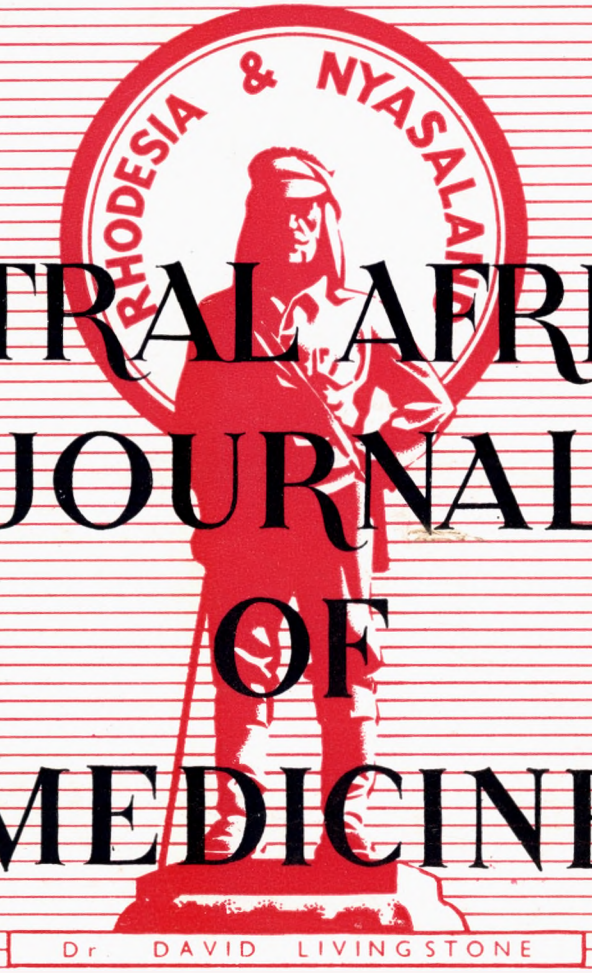
The CENTRAL AFRICAN JOURNAL OF MEDICINE



Vol. 4. No. 5. MAY, 1958.

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PUBLISHED MONTHLY, ANNUAL SUBSCRIPTION £2 2s. 0d.
Registered at the General Post Office as a Newspaper.

The Medical Treatment of Systemic Hypertension

BY

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The diastolic blood pressure is the product of the cardiac output and the peripheral arteriolar tone. A resting level in excess of 100 mm. Hg. means that systemic hypertension is present. As such it contrasts with systolic hypertension, which is the reflection of stroke volume and rigidity of the aorta. It is important to emphasise this difference, for treatment when necessary is directed to the lowering of diastolic pressure. Bright's (1827, 1835) original observations called attention to the kidney, when cardiac hypertrophy was not associated with valvular disease. Mahomed (1879) was among the first to measure blood pressure in Bright's disease, using a modified Marey's sphygmograph. Towards the turn of the century Tigerstedt and Bergmann (1898) isolated from the renal cortex a pressor substance which they named renin. It was not, however, until 1934 that Goldblatt *et al.* produced hypertension in dogs by constriction of the renal arteries. Subsequently Wilson and Byrom (1939) caused hypertension in the rat by constriction of one renal artery. If the constriction was short-lived the hypertension was relatively mild and the histological changes in the arteries similar to those in human benign hypertension; the condition was reversible. If, however, the constriction was maintained the hypertension became severe and was similar to human malignant hypertension. with fibrinoid arteriolar necrosis and intimal proliferation. Removal of the clamped kidney did not in these circumstances affect the course of the hypertension, the perpetuation of which was attributed to arteriolar changes in the unclamped kidney. Of importance was the finding that the clamped kidney showed no arteriolar lesions, presumably as it was protected from the hypertension. It seemed, therefore, that renal ischaemia caused hypertension and that if severe, arteriolar lesions resulted and that these, when renal, perpetuated the condition. A mechanism involving the interaction of renin and hypertensinogen yielding hypertensin, which in turn was broken down by hypertensinase, seemed likely. Yet in chronic hypertension, and apart from the early stages of renal artery constriction. no increase in renin or hypertensin in the renal vein is found. Pickering (1945) has shown in the rabbit, from which one kidney was removed, that the malignant type of hypertension from renal artery constriction persists during survival in spite of nephrectomy, suggesting some extra-renal mechanism for its perpetuation. Although the original rise in blood pressure is probably humoral in renal disease, we remain ignorant of the method of its perpetuation; but once the blood pressure has been raised for a considerable time it seems that the pressure regulation becomes fixed at a higher level and remains so, in spite of the removal of the original stimulus (aortic coarctation, chromaffinoma, unilateral pyelonephritic kidney).

Excessive circulating nor-adrenaline will produce diastolic hypertension; such can be shown experimentally, and in fact occurs in man with phaeochromocytoma. Marked increase in excretion of pressor amines in the urine is present. The hypertension may be sustained rather than paroxysmal. Such a mechanism long continued is obviously rare.

Retention of the sodium ion, either from overdosage of desoxycorticosterone or from an adrenal cortical tumour, in which potassium is lost in quantity, as in primary aldosteronism, is associated with reversibly raised blood pressure. Whereas renal ischaemia and sodium retention are both important in hypertension, we remain ignorant of the mechanism underlying primary hypertension and that perpetuating the condition in the secondary varieties. In consequence, treatment is perforce empiric and often unsatisfactory. However, an appreciation of the known factors as well as the gaps in knowledge may be of help in the planning of treatment.

Hypertension may be classified as in the table. Whether essential hypertension is considered an entity on its own or, as seems more likely and according to Pickering (1955), the upper end of a distribution curve, the outcome of genes and environment, a matter of degree rather than kind, does not influence the question of treatment, but it is of importance that the hypertension is assigned its true aetiology. Hypertension under 40, without a suggestive family story, is not likely to be of the primary variety, and malignant hypertension under 40 is usually nephritic or pyelonephritic. Examination of the urine, the blood chemistry, an intravenous pyelogram and rarely the estimation of the urinary pressor amines will usually suffice for diagnosis. Where there is not a removable cause the severity of the hypertension, no matter the aetiology, must be assessed in regard to available treatment.

Classification of Systemic Diastolic Hypertension (modified from Pickering, 1955).

Primary.

Secondary. Renal—

- Acute and chronic Type I nephritis.
- Late Type II nephritis.
- Chronic pyelonephritis.
- Obstructive lesions with secondary infection.
- Polycystic kidneys.
- Vascular lesions of the kidney.
- Amyloid kidney.
- Radiation kidney.

Endocrine—

- Cushing's syndrome.
- Aldosteronism.
- Phaeochromocytoma.
- Toxaemia of pregnancy.
- Post-toxaemic hypertension.

Arterial—

- Coarctation of the aorta.
- Polyarteritis nodosa.
- Lupus erythematosus diffusa.

The blood pressure may be reduced by sedation, weight reduction, sodium restriction, drugs and rather rarely by lumbo-dorsal sympathectomy and bilateral adrenalectomy.

Sedation will mitigate the overlay of anxiety and thereby lower blood pressure, but if the hypertension is considerable, sedation alone will be of limited value. Weight reduction in the obese hypertensive (particularly female) is of the utmost importance, but again it will not markedly influence severe hypertension. It is, however, to be encouraged. An additional reason is the possible arrest of atheroma. A fat arm gives an unduly high blood pressure reading and some of the pressure lowering from diet may be from simple alteration of this factor. The merits of sodium restriction have been over-rated. To be effective the diet should contain not more than 0.5 gm. sodium daily. To maintain a patient on such a diet indefinitely is well-nigh impossible. Compromise whereby salt is avoided in cooking is quite valueless, and ion-exchange resins are difficult to control over long periods. This brings us to the hypotensive drugs, which hold so much promise yet so frequently disappoint by their side-effects, but which nonetheless represent a tremendous advance in the treatment of the most severe grades of hypertension. The ideal hypotensive drug should be consistently effective by mouth over a period of about eight hours and should be free from side-effects. No such preparation is currently available. The hypotensive drugs may be classified as follows:

(a) Those with mainly central action: 1-hydrazinophthalazine, dihydrogenated ergot, *veratrum viride*, thiocyanate and *Rauwolfia serpentina*.

(b) Those with peripheral effect: dibenamine, benzylimidazoline and phentolamine.

(c) Those blocking ganglionic transmission: tetraethylammonium, pentamethonium, hexamethonium, pentapyrrolidinium, "ecolid" and mecamylamine.

From such a list the anti-adrenaline substances dibenamine, benzylimidazoline and phentolamine can be excluded as unsuitable. Benzylimidazoline is used as a peripheral vasodilator and phentolamine as a test of circulating nor-adrenaline. Dihydrogenated ergot produces vasodilatation with bradycardia, but is effective for a short while only, due to the rapid development of tolerance. The thiocyanates require frequent estimation of the blood level, which should be maintained between 8 and 12 mg./100 ml.; they are erratic in action. The side-effects are rashes, nausea, anorexia, drowsiness and confusion. Sodium nitroprusside has similar toxicity. The hypotensive properties of *veratrum viride* have long been known (Douthwaite, 1928), but its general use awaited the preparation of standardised, stable, reproducible mixtures of the ester alkaloids. Veratrum yields hypotension, bradycardia and emesis through its action on the central nervous system and the vagal nerve endings. Most of the arteriolar dilatation is central in origin, and in practice the von Bezold reflex is unimportant. The bradycardia is abolished by atropine, without return of the blood pressure to its former level. With oral administration Kauntze and Trounce (1951) found that the blood pressure could be lowered in two-thirds of cases, yet that in half of these toxic symptoms were an insuperable bar to continuing treatment. In the remaining quarter, although toxic symptoms were not uncommon, veratrum appeared to be a fairly satisfactory hypotensive. Review of such patients after 3½ years showed the survivors either changed to parenteral hexamethonium or with blood pressures, which, although not normotensive, were relatively stable without treatment. The patients who responded well appeared to be those whose hypertension was not rapidly progressive; in

fact, a group in which treatment is not necessarily indicated. The toxic effects of veratrum are unfortunately inseparable from the hypotensive properties, even with the pure alkaloid germitrine.

1-Hydrazinophthalazine

1-Hydrazinophthalazine (hydrallazine) lowers blood pressure and concurrently increases renal blood flow; this is without change in the glomerular filtration rate, and is less than proportionate to the tachycardia and increased stroke volume. Such may precipitate angina pectoris when coronary atheroma is already present (Harris and Turner, 1954). Hydrallazine has the interesting property of neutralising certain humoral pressor substances such as hypertensin and pherentasin. Partial tolerance to the drug is rapidly acquired and prolonged oral treatment has been unsatisfactory. It is now more usual to give hydrallazine in combination with rauwolfia, hexamethonium or pentapyrrolidinium. Rauwolfia as reserpine is given as 1.5-1.0 mg. daily in divided doses for a fortnight; then hydrallazine is added, beginning with 100 mg. a day and gradually increasing as necessary. Alternatively pentapyrrolidinium or hexamethonium is given orally at eight-hour intervals, the latter as the chloride or by subcutaneous injection, then hydrallazine added and gradually increased. Schroeder *at al.* (1953) have combined oral hexamethonium and hydrallazine with success; it has the dangers inherent in oral hexamethonium. Headache and weakness as well as palpitation from tachycardia due to hydrallazine may be temporarily troublesome. Rarely, with high and prolonged dosage, a condition similar to lupus erythematosus diffusa has been reported (Morrow *et al.*, 1953); the syndrome has rapidly cleared with cessation of hydrallazine.

Rauwolfia serpentina (Reserpine)

Vakil (1940) reported favourably on the hypotensive properties of *Rauwolfia serpentina*, and Arnold and Bock (1953) stressed the hypotension, bradycardia and emotional calm with trivial side reactions. Doyle and Smirk (1954), using large doses of reserpine (2 to 3 mg. t.d.s.), produced some remarkable falls in diastolic blood pressure, but found nasal and conjunctival congestion, flushing, somnolence, fatigue and depression troublesome. The occurrence of depression, even with suicidal tendencies, is mainly in those already showing signs of this affective disorder, but may crop up suddenly under higher dosage in the mentally stable. High dosage is therefore to be avoided. In my hands 1.5 to 2 mg. reserpine daily has been somewhat unpredictable. The drug is, however, useful in augmenting a more potent hypotensive and in its production of bradycardia. It is usual to start with 1.0-1.5 mg. reserpine daily, thence to add hydrallazine or pentolinium orally until adequate control of blood pressure short of side-effects occurs. There is no doubt of the frequent, although variable, additive or synergistic action of reserpine; particularly in association with ganglionic blockade, it smoothes out the peaks and troughs of hyper and hypotension.

Methonium Compounds

The pharmacology of the methonium salts has been described by Paton and Zaimis (1948), and their circulatory effects by Arnold *et al.* (1949). They block intra-ganglionic transmission, probably by combination with a receptor substance, and thereby cause splanchnic and peripheral arteriolar dilatation. The hypotension is in part orthostatic and may be neutralised by binders and bandages; there is associated tachycardia. In recumbency the cardiac output is slightly diminished, coronary artery flow unimpaired and renal blood flow after the preliminary decrease returns to normal. Alteration in organ blood flow may persist after the hypotensive effect has ceased. The block occurs both in sympathetic and parasympathetic transmission, and although the degree of parasympathetic involvement varies with the particular compound, it is never sufficiently in abeyance not to cause symptoms.

Hexamethonium

Hexamethonium is a more effective hypotensive than tetraethyl ammonium or pentamethonium. The bromide salt is more soluble than the chloride or bitartrate and therefore more readily absorbed from the gut; but even with meticulous care in the amount and spacing of doses, the rate of absorption is variable. Interference with parasympathetic transmission may diminish the tone of the gut to a degree of ileus, which allows continuous and therefore excessive absorption; dangerous hypotension results, in which intravenous nor-adrenaline may prove ineffectual. Latent pyloric obstruction may become complete; laporotomy has been misguidedly performed on account of the intestinal obstruction from ileus. Prostatic obstruction may also be troublesome from parasympathetic depression. Bromism is a possible danger. No such objections can be levelled at subcutaneous

injection, which in the absence of circulatory failure ensures absorption and yields a reproducible effect from one to four hours thereafter. I do not think there is now any place for oral hexamethonium in the treatment of hypertension.

The inception of treatment with hexamethonium entails admission to hospital. During the investigation of renal and cardiac function and other special investigations, the blood pressure is recorded four times daily; this gives a base line for subsequent appraisal. A test dose of 25 mg. hexamethonium chloride is given intravenously and the response of the patient's blood pressure is recorded in the erect and recumbent positions. If the fall in diastolic pressure is trivial, then 50 mg. is given intravenously the next day. From such findings the patient's suitability and the dosage are assessed. Usually a start is made with 25 mg. subcutaneously at eight-hourly intervals, and this is increased as tolerance develops, the evening injection being the largest, until the diastolic pressure erect is between 100 and 110 mm. Hg. three hours after injection. The patient may need to sit or lie for thirty minutes or so after each injection, but should as far as possible be propped up or ambulant to benefit from the orthostatic hypotension.

It may take a month before stability of dosage is achieved, and as much as 750 mg. may be needed during the 24 hours. The patient readily learns to give his own injections. Subsequently checks at monthly intervals are essential, otherwise the occurrence of hypotensive symptoms gives a rough guide to the efficacy of dosage. Although control in hospital was often good, such was not the case in out-patients in my experience.

Pentapyrrolidinium (Pentolinium Tartrate)

Pentolinium is a bisquaternary ammonium compound with some structural similarities to hexamethonium. It blocks both sympathetic and parasympathetic ganglionic transmission without discrimination. Its hypotensive activity is four to six times that of hexamethonium and its effect longer. The clinical use has been reported by Smirk (1953). The variability of intestinal absorption makes any sustained control of severe hypertension unlikely when pentolinium tartrate alone is given by mouth. In this connection reserpine may be of help, and when there is no urgency treatment should start with reserpine 0.5 mg. twice daily, the maximal effect of which will be apparent in two weeks. Thence pentolinium 20 mg. is given half an hour before breakfast and dinner. The doses are increased by 20 mg. at daily or less frequent intervals, until there is slight faintness on standing three hours or so after ingestion. The development of tolerance will soon remedy this, and the dosage will need further adjustment aiming at a diastolic blood pressure erect of about 100 mm. Hg. It must be emphasised that dosage in the individual is critical, that absorption is quickened if the drug is taken in solution and fasting, that its effect may persist for twelve hours, in which case hypotensive symptoms may occur after breakfast due to cumulation, but that the interval between doses in some patients should be only eight hours and that the individual doses may differ in amount, depending on the blood pressure readings. Reserpine is continued, for it undoubtedly smoothes out the hypertensive peaks. The bowels must be evacuated daily and a regular aperient ensures a margin of safety; but if constipation occurs, then pentolinium must be withheld until the condition is rectified. Enemas are to be avoided.

Whereas the success of oral pentolinium, even with reserpine, in severe hypertension is speculative, by subcutaneous injection it is in my opinion the drug of choice. The effective action lasts about six hours and this can be prolonged by solution with ephedrine or combination with oral reserpine 0.5 mg. twice daily. It is usual to start with 2.5 mg. pentolinium subcutaneously at 8 a.m.; the afternoon dose is smaller and the evening larger. The amounts are gradually increased or the interval shortened from eight to six hours until tolerance develops and the diastolic blood pressure is maintained below 120 mm. Hg. and standing is not lower than 80 mm. Hg. Side effects are an inevitable concomitant of adequate treatment. Initial treatment is best undertaken in hospital, where blood pressure records hourly, standing or sitting, are a great help. Subsequently the patient is re-assessed at weekly and later monthly intervals. This can only be satisfactorily undertaken in a special clinic, but the lack of such ideal facilities does not mean that treatment with subcutaneous pentolinium should be withheld.

Mecamylamine

Mecamylamine is a secondary amine, well absorbed from the gut and excreted slowly, mainly (60 per cent. to 80 per cent.) in the urine. The hypotensive action lasts from 12 to 24 hours, and reserpine potentiates this. I

have used such a combination by mouth in hypertension complicating pregnancy and in very moderate hypertension, with quite gratifying results. But in higher dosage side effects have been frequent and troublesome.

SIDE EFFECTS

Temporary undue hypotension is inevitable during treatment, vasodilatation from fever, hot weather or considerable exertion, or depletion of the sodium ion may predispose to this. Yawning, dizziness, nausea, amblyopia, facial pallor or syncope are indicative of such hypotension and are aggravated by standing still. Usually lowering the head in recumbency is sufficient; but if parasympathetic paresis of the gut causing excessive and continuing absorption of the drug, or actual overdosage parenterally are responsible, then intravenous nor-adrenaline or methylamphetamine may be necessary and neostigmine should be given in ileus.

Paralysis of accommodation tends to lessen with continuing treatment; tinted spectacles or eserine drops may be helpful. Mouth dryness is in part relieved by lemon and chewing gum; carbachol has been used. Constipation is not often troublesome with parenteral pentolinium. Previously symptomless pyloric stenosis, prostatic hypertrophy or glaucoma may become prominent during treatment and cause temporary discontinuance. Diminution of libido with ganglionic blockade is not uncommon; it is beneficial.

Dissecting aneurysm of the aorta has been found at necropsy in nine of 44 hypertensive patients treated with hexamethonium or pentolinium (Beaven and Murphy, 1956). This high incidence may be due to the very considerable daily swings of blood pressure during treatment, when medial degeneration of the aorta is already present.

INDICATIONS FOR TREATMENT

Before subjecting a patient to a regime which is not merely unpleasant but potentially dangerous and rarely lethal, it is well to have in mind what advantages both immediate and long term are to be gained, and thence to decide the particular merits of treatment. Primary hypertension probably becomes malignant in less than 1 per cent.; it is less harmful in woman. But where the diastolic level is rapidly rising whilst under observation and in man reaches 130 mm. Hg. under age 45, or 140 mm. Hg. in woman, the level must be persistently lowered. The appearance of fluffy retinal exudate presages the malignant phase. Such exudates are presumably from oedema and are an expression of the absolute height of the diastolic blood pressure and the speed at which it has risen; they may be associated with detachment of the retina. They are quite different from the hard, ischaemic exudate arising afresh or following the resolution of haemorrhage, and the yellow exudate of diabetes mellitus. That the malignant phase demands immediate hypotensive treatment needs no emphasis; such treatment first with sympathectomy and later with hexamethonium and pentolinium has considerably, although usually only temporarily, improved the prognosis. As fibrinoid necrosis in the renal arterioles tends presumably to establish a vicious circle of ischaemia, treatment should be begun early. Yet even with patients under bi-monthly supervision, considerable renal damage may be already evident when first the malignant phase is diagnosed. Most patients under 45 years have chronic pyelonephritis or chronic nephritis underlying their malignant hypertension and tend to have lower diastolic pressures than the primary type. Considerable renal damage entails much caution over treatment. Hypertensive encephalopathy, beautifully shown by Byrom (1954) to be from diffuse arterial spasm, precipitated by sudden upsurges of blood pressure, needs immediate hypotensive treatment, whether accompanied by renal impairment slight or gross.

The basic factors underlying heart failure are excessively increased filling pressure, myocardial failure and increased peripheral resistance, either systemic or pulmonary. Not a few patients present with left ventricular failure as the first manifestation of their hypertension. Such will reap much benefit from a lowered blood pressure.

Treatment is imperative in pregnancy with hypertension, both in the production of a living baby and the protection of the mother from eclampsia.

In summary these are in my opinion absolute indications for treatment with hypotensive drugs:

(1) The malignant phase or the threat of its occurrence (a rapidly rising diastolic level, particularly under 45 years and where there is not a removable cause).

(2) Hypertensive left ventricular failure.

(3) Hypertensive encephalopathy.

(4) Hypertension in pregnancy.

I have purposely made the indication for treatment severe hypertension, with the exception of that in pregnancy. There is no evidence that

lowering blood pressure in mild or moderate hypertension will modify the course of the condition. Sudden deterioration in the majority of primary hypertensives is uncommon, and unfortunately there is no way of foretelling those in whom it will happen. All effective hypotensive treatment, other than diet, is attended by distressing side-reactions, and where benefit is unlikely, to subject a patient to such measures is unjustifiable. What of moderate hypertension with recurrent headache? Hypertensive headache is typically occipital and nuchal in situation, present on waking and disappearing as the day draws on. It is unusual with a diastolic pressure below 120 mm. Hg. and frequently absent with a diastolic level of 140. Such headaches will often respond to sleeping with the head higher, weight reduction and codein; if not, then oral mecamylamine given twice daily may be of help. It is a matter of importance to distinguish the neurotic headache from the organic, and attention to the history will usually make this obvious.

If moderate hypertension (unless complicated) is not to be treated, it is equally important that where the indications for treatment are clear cut. such treatment should be both continuous and effective.

Type of Treatment

Hypertension in pregnancy, when of slight to moderate severity, that is, with a diastolic up to 120 mm. Hg. and where the life of the foetus is in jeopardy, will probably respond well to a combination of oral mecamylamine with reserpine. This should be continued throughout pregnancy and the puerperium. There is no point in prolonging treatment afterwards if the diastolic is relatively fixed. If the hypertension is of a progressive nature, this will be apparent during the pregnancy, when control with mecamylamine and reserpine will be inadequate.

In severe hypertension, with the complications I have stressed, persistent lowering of the blood pressure is essential for survival, and for most of the day the diastolic should be around 100 mm. Hg. At present pentolinium is the most suitable drug for parenteral administration. The daily vagaries of intestinal absorption are such that effective control over dosage in amount and time is only possible by injection. The subcutaneous route is the better. Injections may be thrice or twice in the day and the dose before retiring should be the largest. Reserpine is given orally for its adjuvant effect. The preliminary treatment, during which dosage is assessed, is best carried out in hospital, where sufficient blood pressure records are available, the patient is encouraged to be ambulant as far as possible to benefit from the orthostatic hypotension and conversely where medical assurance is available should the blood pressure fall too low. Flat recumbency and the avoidance of heating are sufficient, unless the hypotension is very gross, in which event nor-adrenaline or methylamphetamine intravenously will be needed. Peripheral circulatory failure makes intramuscular injection impracticable.

The patient soon learns to give his own injections. The original period in hospital must be adequate for stabilisation of dosage; subsequent supervision is best in special clinics, where ideally the blood pressure range over a whole day is recorded. Such is rarely possible, nor is control of the blood pressure likely to be absolute, yet in the majority it is adequate.

Wagener and Keith (1924) reported the death of their original 14 patients with malignant hypertension between one and 44 months after diagnosis. Such a prognosis has been remarkably changed, first by lumbodorsal sympathectomy and later by the methonium compounds; McMichael (1955) reports a two-year survival in 43 per cent. of 32 patients treated with methonium compared with 7 per cent. of 30 untreated patients. The main factor in survival is that treatment should be instituted before renal damage is severe; after two years' survival the chances improve.

Hypertensive encephalopathy can be controlled and hypertensive left ventricular failure is alleviated by parenteral pentolinium. The outcome in both is mainly dependent on the condition of the cerebral or coronary arteries.

Certain severely hypertensive patients with adequate renal function cannot be controlled by ganglionic blockade. In some I have recommended lumbodorsal sympathectomy, after which adequate lowering of blood pressure by methonium salts has been obtained. Some patients will not tolerate daily injections, and for these lumbodorsal sympathectomy may be desirable. I have twice recommended bilateral adrenalectomy in patients (both women) with unresponsive hypertension and angina decubitus; although this has meant substitution therapy, the results have been in the circumstances satisfactory.

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